

# EXHIBIT 2

## THE GASTROINTESTINAL SYSTEM: AN INTRODUCTION

### INTRODUCTION: CARNIVORES, OMNIVORES AND HERBIVORES

The chapters making up this section of this book are concerned with various aspects of the mammalian gastrointestinal system. It is a complex topic which can be broken down into a number of subjects which form the subsequent chapters in this section. However, if we compartmentalise the topic too much we may lose sight of the wood for the trees. This chapter aims to introduce the gastrointestinal physiology of domestic animals by means of a broad overview of structure and function ("What do they do and how do they differ?"), in order to provide a grounding for the more detailed descriptions that follow in later chapters.

A major reason why human beings keep domestic mammals (excluding cats and dogs) is their ability to convert food which humans find inedible - or at least unpalatable - to food (meat or milk) which humans can eat. The proteins, fats and carbohydrates needed in the diet of higher animals are found in nature only as part of, or in association with, living matter; higher animals therefore depend on plants and/or other animals for their nutrition. The dietary habits of domestic animals range from flesh-eating (carnivore) to plant-eating (herbivore). The anatomy and physiology of their digestive tracts differ in the extent to which certain features, present in all species, are developed.

Digestion is the process of converting food into an absorbable form. Effective digestion of plant food requires a means of dealing with the most important structural material of plants, cellulose - a carbohydrate polymer which is extremely insoluble and remarkably resistant to chemical attack. Cellulose digesting enzymes, cellulases, are present in the intestinal tract of several invertebrates that feed on wood and similar plant products. These enzymes are, however, absent for some reason from the digestive secretions of vertebrates, and yet many vertebrates digest cellulose and depend on it as their main energy source; they can do so because, within their gut, are found symbiotic micro-organisms which can digest cellulose.

Many mammals are herbivores, and most herbivorous mammals live on a diet that makes cellulose digestion essential. The ruminants, which include some of our most important domestic meat- and milk-producing animals - cattle, sheep and goats - have a specialized digestive tract which is highly adapted to symbiotic cellulose digestion. However, a large number of non-ruminant mammals also depend on symbiotic micro-organisms for cellulose digestion, although their anatomical adaptations differ from those of the true ruminants. Digestion of cellulose in the plant diet by microbial enzymes in adult cattle, sheep and goats on a normal diet occurs in the forestomach, of which the rumen is the largest compartment; this organ therefore serves as the major source of energy in those species. It serves a function similar to that of the large intestine in horses. The domesticated herbivores fall into two groups: (1) those with rumens (e.g. cattle, sheep and goats) in which extensive microbial fermentation of the plant diet occurs in a specialized region of the digestive tract prior to digestion by alimentary enzymes; and (2) those with simple stomachs (e.g. horse), in which microbial fermentation takes place in the distal part of the digestive tract.

Plant material is lower than meat in energy content, and the herbivore must consume a large quantity in order to satisfy its energy requirements. Herbivores spend much more time eating than do carnivores; in grazing ruminants, eight or more hours per day may be spent in eating. Rumination may take an equally long period. This type of feeding is associated with the essentially continuous activity of the secretory glands and musculature of the tract. Thus the ruminant abomasum normally secretes acid gastric juice continuously because the flow of ingesta from the reticulorumen into the abomasum never ceases. If herbivores such as the pony are fed a concentrated feed once or twice daily, the secretory and motor activity of their GI tract will be cyclic; on the other hand, if a pony is maintained on pasture, it will graze for a considerable proportion of each 24 hours, and its gastrointestinal activity will be more continuous.

Herbivores need to maintain continuous fermentation and absorption in those parts of the GI tract where cellulose-containing materials can be broken down. Functional differences between species can be related to the rates at which digesta pass through the different parts of the tract. Efficient digestion (particularly microbial digestion) and absorption depend on an adequately slow movement of digesta through the tract; movement of digesta through the large intestine in a non-ruminant herbivore, such as the horse, is much slower than in a carnivore, such as the dog.

Carnivores obtain most of their food by eating other animals, and their digestion relies largely on enzymes rather than micro-organisms. Microbial digestion of cellulose occurs in the colon of the dog, but to such a small extent that the colon can be removed and the dog can survive perfectly well.

Omnivores feed on both plants and animals, but their digestion is mainly enzymatic - like that of the carnivores. The pig is usually considered to be an omnivore, but under domestication is mainly herbivorous; in addition to its enzymatic digestion, a

good deal of microbial breakdown of plant material occurs in the large intestine of the pig, and also, to a lesser extent, in its stomach.

The small intestine of all mammals digests soluble carbohydrate, fat and protein, but cannot digest cellulose. The dog on a normal diet depends almost entirely on its small intestine for its nutrition. The small intestine of the horse would not be capable of digestive activity similar to that in the dog, even if the horse were fed with a dog's diet. The omnivorous pig can adapt to either a carnivorous or a herbivorous diet.

The physiological mechanisms required to support cellulose digestion are quite different from those needed for the digestion of meat. Furthermore, the systems needed in the early life of a particular species for the digestion of milk will be very different from those needed later in life for solid foods.

## GROSS STRUCTURAL DIFFERENCES IN MAMMALIAN GI TRACTS

Figure 1 illustrates the GI tracts of various mammals, and demonstrates the influence of dietary habit upon structure. The relative capacities of different compartments in different species are listed in Table 1.

### ADD TABLE 1

An extreme example of a carnivore is provided by the mink with a simple (noncompartmentalized) stomach and a short intestine. The terminal segment of the intestine (what in most species would be called the "large intestine") is larger than the upper (or "small") intestine, but it is nonsacculated and contains neither a caecum nor any evidence of a sphincter or valve at its junction with the "small" intestine. The digestive tract of the dog is also short and simple, but it does contain an ileocaecal valve and a small caecum. The pig has a simple stomach, but both its small and large intestine are longer than those of the mink or dog; furthermore the pig caecum and part of the pig colon are sacculated as a result of the presence of longitudinal bands of muscle. These sacculations, or haustra (buckets), may serve to prolong the retention of ingesta. The horse stomach is similar to that of the pig, but the small intestine of the horse is relatively much shorter, and its caecum and colon have a much larger volume. The small intestine of the sheep is relatively longer than that of any other common domestic or laboratory animal, but neither its caecum nor its colon is sacculated or particularly voluminous. The sacculated appearance of the lower colon and the rectum in the sheep is due to the presence of faecal pellets.

The species discussed illustrate the variation in the mammalian GI tract. Parallel changes have developed within the marsupials and within a number of different placental mammals. Thus the marsupial stomach can range from simple (opossum) to complex (kangaroo), a range similar to that seen within the order Artiodactyla (exemplified by the pig and the sheep). Other mammalian orders e.g. bats, edentates, rodents, and primates, also contain species with simple and complex stomachs, and differing large intestinal structure.

### *Capacity of gastrointestinal organs*

Table 1 lists some species variations in the dimensions and capacity of various segments of the GI tract. They were based on postmortem examination of tissues, which may have undergone exchange of water between gut contents and body fluid spaces, and furthermore the volume of digesta in different parts of the tract can vary greatly according to the time after feeding. Nonetheless the figures are sufficiently different to emphasize the marked differences between species.

## OVERVIEW OF GASTROINTESTINAL FUNCTION

The two main functions of the gastrointestinal (GI) tract are digestion and absorption. The mucosa should discriminate against the absorption of toxic substances. The cells lining the gastrointestinal tract perform digestion, secretion and absorption. They possess enzymes which can digest sugars and peptides, and they can transport specific substances present in the intestinal lumen. The membranes and junctional complexes between the cells serve as a barrier to many water soluble substances; specific transport processes are therefore required for those which are to be absorbed. Prior to absorption, many dietary constituents must be degraded in the intestinal lumen into substances which can interact with digestive enzymes or transport processes in intestinal cells. This luminal digestion requires a specific luminal environment which is achieved by secretions of accessory organs (salivary glands, pancreas, and liver) and the gut mucosa itself. Together these secretions provide electrolytes, water, acid, base, digestive enzymes, and bile salts which are necessary for luminal digestion in an optimal environment. This secretory function is an energy-requiring process and is under neural and endocrine control.

An important component of digestion and absorption is transit. Luminal contents must be shifted along the length of the tract at a rate appropriate to the digestive and absorptive processes occurring in each part of the tract. This transit is achieved by the motility of the gut, which, like secretion, needs energy and is controlled by nerves and hormones.

The digested nutrients must be absorbed by the gut epithelium and transferred to the circulation. It is equally important to reabsorb the various secretions provided by the accessory glands and gut mucosa. Very large quantities of water and electrolytes are secreted into the lumen of the digestive tract (especially in herbivores); if they were not reabsorbed, dehydration and circulatory collapse would soon follow.

In summary, the primary functions of the gastrointestinal system are digestion and absorption; secretion, motor activity, and reabsorption are essential components of the two primary functions.

## GASTROINTESTINAL FUNCTION IN HERBIVORES

Cellulose-containing feed is mostly bulky, and the processes involved in its digestion are relatively slow and take time. Much space is therefore required, and the part of the digestive tract used for cellulose digestion is therefore large and possesses several compartments. Herbivores may be divided into ruminants and non-ruminants; some non-ruminants exhibit a behavioural specialization (coprophagy) which is discussed below.

Ruminants are the most diverse (about 155 species) and best known of herbivores in which extensive fermentation occurs before, rather than after, exposure to acidic gastric secretion. A ruminant-like fermentation also occurs in the Tragulidae (chevrotains) and Camelidae (e.g. camel and llama); members of these families have complex three-chambered stomachs. Other animals in which there is evidence for a complex cellulose-digesting microbial population in the foregut include hippopotamuses, tree sloths, leaf-eating monkeys of the subfamily Colobinae, and the macropod marsupials (e.g. kangaroos).

### *Ruminants*

A ruminant is an animal that chews the cud, cud being defined by the Shorter Oxford Dictionary as "the food which a ruminating animal brings back into its mouth from its first stomach and chews at leisure." In ruminants, the stomach consists of several compartments; to be precise, the true digestive stomach (the abomasum) is preceded by several large compartments, reticulum, rumen and omasum. The rumen serves as a large vat in which the food, mixed with saliva, undergoes extensive fermentation - "a slow decomposition of organic substances induced by micro-organisms". Large numbers of both bacteria and protozoa are found in the rumen. These micro-organisms are responsible for the breakdown of cellulose, the breakdown products becoming available for further digestion. The fermentation products (mostly acetic, propionic, and butyric acids) are absorbed and utilized; carbon dioxide and methane (CH<sub>4</sub>) formed in the fermentation process escape by belching (eructation). Rumination, evident as "chewing the cud", involves the regurgitation and re-chewing of undigested fibrous material, which is then swallowed again. As the food re-enters the rumen it undergoes further fermentation. Broken-down food particles gradually pass to the other parts of the stomach where they are subjected to the usual digestive juices in the abomasum (or "fourth stomach" - which corresponds to the digestive stomach of other mammals).

The fermentation products are mostly short-chain organic acids, and the enormous amounts of saliva secreted by ruminants serve to buffer these acids in the rumen. The saliva of ruminants is mainly a dilute solution of sodium bicarbonate, and serves both as a buffer and as a suitable fermentation medium for the micro-organisms. The ruminant secretes an impressive volume of saliva. The total secretion of saliva per day has been estimated at 6 to 16 litres in sheep and goats, and at 100 to 190 litres in cattle. Since sheep and goats weigh about 40 kg, and cattle some 500 kg, the daily production of saliva may reach roughly one-third of the body weight. Since two-thirds of the body weight is water, about half the total body water passes through the salivary glands (and the rumen) each day.

The rumen protozoans include ciliates which superficially resemble free-living forms such as *Paramecium*. Several hundred thousand protozoa are found in each millilitre of rumen contents. Many of the rumen organisms have been cultured in the laboratory, and extracts from pure cultures show cellulase activity. The ciliates are obligate anaerobic organisms which must meet their energy requirements through fermentation processes. This yields relatively little energy for the micro-organisms, but it means that the fermentation products become available to the host animal, which in turn uses them in oxidative metabolism. Since symbiotic cellulose digestion is the only way that cellulose becomes available to mammals, the relatively small energy loss to the symbiotic micro-organisms is a small price to pay.

Rumen micro-organisms contribute in several other ways to the nutrition of the host. They can synthesize protein from

inorganic nitrogen compounds, such as ammonium salts. Urea, normally an excretory product eliminated in the urine, can be added to the feed of ruminants and increase the protein synthesis. This has been used in the dairy industry, for urea can be synthesized cheaply, and it is less expensive to supplement the diet of milk cows with urea than to use more expensive high-protein feed.

The rumen contents of a cow may weigh as much as 100 kg, with a total weight of protozoans of about 2 kg, containing 150 g of protozoan protein. About 70 percent of the protozoan population passes into the omasum each day - a protein supply of over 100 g per day.

Microbial protein synthesis in the rumen is especially important when the animals are fed on low-grade feed. Camels fed on a nearly protein-free diet (inferior hay and dates) excrete virtually no urea in the urine. Urea continues to be formed in metabolism, but instead of being excreted, this 'waste' product re-enters the rumen, in part through the rumen wall and in part through the saliva. In the rumen, the urea is hydrolyzed to carbon dioxide and ammonia, the latter being used for resynthesis of protein. In this way a camel on low-grade feed can recycle much of the small quantity of protein nitrogen available to it. Similar re-utilization of urea nitrogen in animals fed on a low-protein diet has been observed in the sheep.

If inorganic sulphate is added to the diet of ruminants, the microbial synthesis of protein is improved; the sulphate is incorporated into the important amino acids cysteine, and methionine, which are both essential amino acids. Thus, the rumen micro-organisms contribute to both protein synthesis and the quality of the protein. Because the microbes in the rumen can synthesize all the essential amino acids, ruminants are nutritionally independent of these amino acids, and the quality of the protein they receive in their feed is therefore not very important.

Another nutritional advantage of ruminant digestion is that some important vitamins are synthesized by the rumen micro-organisms. This applies to several of the vitamin B group; in particular, the natural supply of vitamin B12 for ruminants is obtained entirely from micro-organisms.

*In conclusion*, the major advantages of the ruminant arrangement (i.e. pregastric fermentation) are as follows:

1. Microbial products of value to the host (e.g. VFAs and B vitamins) are presented to efficient absorptive sites in both the rumen and lower bowel.
2. Ammonia and substances that are metabolized to ammonia (e.g. urea) are used by the microbes for synthesis of high-quality microbial protein, which is subsequently subjected to gastric and small bowel digestion.
3. Selective retention of particles at the reticulo-omasal orifice, and the added opportunity for mechanical breakdown of fibres during rumination, enhance digestion of coarse foods.
4. The large quantities of gas that are produced may be readily released from the system by eructation (belching).
5. The large input of saliva provides a highly-buffered medium with a consistency that permits effective mixing by ruminal contractions.
6. Toxic substances in the diet may be detoxified during fermentation before exposure to small intestinal absorption.

#### *Non-ruminant mammals*

Cellulose digestion in many non-ruminant mammals is also aided by micro-organisms. In some non-ruminant herbivores, the stomach is large and has several compartments, and the digestion is very similar to that of ruminants, save for the absence of the regurgitation and re-chewing of food which is the distinctive feature of the ruminant. In other herbivorous mammals, the major fermentation of cellulose takes place in a large diverticulum from the intestine, the caecum.

Multiple-compartment stomachs are found not only in some non-ruminant ungulates, but in far-removed animals such as the sloth and the langur monkey. Even among marsupials there are animals, such as the rabbit-sized quokka, with a rumen-like stomach. Amongst domestic mammals, the pig exhibits some bacterial fermentation in its stomach which, although consisting of only a single compartment, has different functional zones within it.

Microbial fermentation in the caecum is similar to fermentation in the rumen, but the rumen has two definite advantages over

the caecum. One is that rumen fermentation takes place in the anterior portion of the gastrointestinal tract, so that the products of digestion can pass through the long intestine for further digestion and absorption. The other advantage of the ruminant arrangement is that the mechanical breakdown of the food can be carried much further; coarse and undigested particles can be regurgitated and masticated over and over again. This difference is clearly visible if we compare the faeces of cattle (ruminants) and horses (non-ruminants). The faeces of the former are a well ground-up smooth mass with few large visible fragments, whereas those of the latter have coarse fragments of the food intact in the faeces.

An improvement in the digestion of plant materials through fermentation is not restricted to mammals. Many birds have two large caeca suitable for cellulose fermentation.

### *Coprophagy*

The disadvantage of locating the cellulose fermentation in the posterior part of the intestinal tract can be circumvented in an interesting way. A number of rodents, as well as rabbits and hares, form a special kind of faeces within the caecum, and these they re-ingest so that the food passes through the entire digestive tract a second time. There are, in fact, two kinds of faeces: the well-known ordinary firm dark rodent faecal pellets, and a softer larger lighter kind which are not dropped by the animal but are eaten directly from the anus. This latter type of faeces is kept separate from the ordinary droppings within the rectum, and their reingestion permits a more complete digestion and utilization of the food.

Coprophagy (from the Greek *copros* = excrement and *phagein* = to eat) is common in rodents, and is of great nutritional importance. For example, if coprophagy is prevented, rats require supplementary dietary sources of vitamin K and biotin. In addition, deficiencies of other vitamins develop more rapidly. Even if rats are provided with a variety of dietary supplements, the growth rate is still depressed by 15 to 25 percent if coprophagy is prevented. If the rats are allowed to eat ordinary rat faecal pellets, but prevented from normal coprophagy (i.e. prevented from eating faeces from their anus), they still do not grow normally.

In rabbits, prevention of coprophagy leads to a decrease in the digestibility of the food, as well as a decrease in protein utilization and nitrogen retention. The special 'soft' faeces which rabbits re-ingest originate in the caecum. When ingested, these faeces are not masticated and mixed with other food in the stomach; they tend to lodge separately in the fundus of the stomach. The soft faeces are covered by a membrane, and they continue to ferment in the stomach for many hours, one of the fermentation products being lactic acid. In this way the fundus of the stomach serves as a fermentation chamber, analogous to the rumen of sheep and cattle, and thus provides important nutritional advantages to the animal.

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